UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/613,380 | 07/03/2003 | Wendell Lim | UCSF03-114 | 5261 |

23379 7590 11/16/2007
RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMEMTE, CA 92672

| EXAMINER | |
|---|---|
| SKIBINSKY, ANNA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 11/16/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number:10/613,380
Filing Date: July 03, 2003
Appellant(s): LIM ET AL.

Richard Aron Osman
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 8/08/2007 appealing from the Office action mailed 7/30/2007.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

No amendment after final has been filed.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Baker et al. "Protein Structure Prediction and Structural Genomics," Science, vol. 294 (2001) pages 93-96.

Clark, "Protien refolding for industrial processes," Current Opinion in Biotechnology, vol. 12 (2001) pages 202-207.

Cummingham et al. "Optimizing synthesis and expression of transmembrane peptides and proteins," Methods, vol. 41 (2007) pages 370-380.

Dueber et al., "Reprogramming Control of an Allosteric Signaling Switch Through Modular Recombination," vol. 301 (2003) oages 1904-1908.

Kim, "Expression and purificaion of recombinant immunotoxin-a fusion protein stabilizes a single-chain Fv (scFv) in denaturing condition," Protein Expression and Purification, vol. 27 (2003), pages 85-89.

Pedalacq et al., "Engineering soluble proteins for structural genomics," Nature Biotechnology, vol. 20 (2002) pages 927-932.

Seffernick et al. "Melamine Deaminase and Atrazine Chlorohydralase: 98 percent identical but functionally different," Journal of Bacteriology, vol. 183 (2001) page 2405-2410.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 2, 6, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an autoregulated fusion protein with an N-WASP output domain, PDZ and SH3 input domains (with the domains in this order in the sequence), wherein the input domains cooperatively regulate the output domain as an AND-gate, does not reasonably provide enablement for any autoregulated protein, including those with all of the output and input domains listed in the Tables of the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification does not provide guidance for predictably making any autoregulated protein with a set of interacting input and output domains other than with an N-WASP output domain and PDZ and SH3 input domains, wherein said domains are in the order such that the N-WASP output domain is linked to the PDZ input domain (specification, page 22, lines 4-6) and the PDZ and SH3 input domains are linked to one another (specification, page 25, lines 17-23). There is insufficient guidance for engineering *any* autoregulated fusion protein that will "allosterically and external, ligand-dependently regulate the output domain.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at

1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims.

(1) the quantity of experimentation necessary to successfully create a polynucleotide chimera that will express a protein is undue. The specification lists a multitude of domains and recites in claim 1 that the protein's input domains will regulate the output domains. The disclosure teaches in the "Detailed Example" (pages 20-27) making a functional autoregulated protein with an N-WASP output domain and SH3 and PDZ input domains. The description does not provide detailed guidance on how to achieve the synthesis of such an autoregulated protein using all of the domains listed in the specification. Furthermore, the claims are directed to *any* autoregulated fusion protein, for which the specification has failed to provide guidance on how to make using the steps instantly claimed.

(2) The description describes generating an autoregulated fusion protein with an N-WASP output domain and SH3 and PDZ input domains. The description does not provide detailed guidance to make and use autoregulated fusion proteins with the other input and output domains listed in the specification or any other conceivable domains.

(3) The description provides a working example describing an autoregulated protein with an N-WASP output domain, SH3 and PDZ input domains. The description

does not provide a representative sample of experiments to cover the multitude of input and output domains that are recited as being able to comprise such an autoregulated protein. The "Detailed Example" is insufficient to describe the making of *any* autoregulated protein for any and only describes one specific autoregulated protein with an N-WASP output domain, SH3 and PDZ input domains.

(4) The nature of the invention is complex and there is insufficient teaching in the specification to enable the making and using of the multitude of potential autoregulated proteins possible with the myriad of combinations of output an input domains listed in the Tables and available to the researcher. There is insufficient teaching in the specification to enable a general autoregulated protein that will "allosterically and external, ligand-dependently regulate the output domain" for all possible protein domains. The only autoregulated protein described in the specification is one with an N-WASP output domain and SH3 and PDZ input domains. The complexity of creating a fusion protein that will function properly as described in claim 1 warrants more guidance in order to enable the invention.

(5) the state of the prior art teaches making fusion proteins but it does not teach autoregulated fusion proteins. The state of the art teaches that there is uncertainty as to whether certain combinations of domains will result in a functioning or soluble fusion protein. For example, Cunningham et al. (Cummingham et al., Methods, vol. 41 (2007) pages 370-380) teach that Trx as a fusion partner is used to overcome the problem of inclusion body formation, which is an indication of inappropriate protein folding. Cunningham et al. further teach that it is generally advisable "to explore potential fusion

constructs of bacterial expression among these options can be unequal." (page 378, col. 1, par 3). This amounts to undue experimentation.

In addition, Kim (Protein Expression and Purification, vol. 27 (2003), pages 85-89) teaches recombinant immunotoxins in which the PE domain has been replaced with the Fv portion of an antibody, forming a fusion protein (Abstract, page 86, col. 1, par 1). Kim teaches that many recombinant immunotoxins have been produced as inclusion bodies and though steps can be taken to solubilize and refold the inclusion bodies, the refolding process does not always produce a native protein and several attempts to refold the scFvs under various conditions yielded very low amounts with poor specific activity (page 88, col. 2, par 2).

Clark (Current Opinion in Biotechnology, vol. 12 (2001) pages 202-207) teaches that expression of genetically engineered proteins in bacteria often results in the accumulation of the protein product in inactive insoluble deposits inside the cell (i.e. inclusion bodies) (page 202, col. 1, par 1).

Pedelacq et al. (Nature Biotechnology, vol. 20 (2002) pages 927-932) teach attempts at protein engineering where protein domains thought to improve solubility were directed into inclusion bodies, expressed in E. coli but nevertheless failed to improve solubility (page 927, col. 2, par 2).

In terms of structure prediction, Baker et al. (Science, vol. 294 (2001) pages 93-96) teach that accuracy of a comparative model is related to the percentage of sequence identity of which it is based, correlating the structure and sequence similarity of two proteins (page 93, col. 3, par 2).

Further, Seffernick et al. (Journal of Bacteriology, vol. 183 (2001) page 2405-2410) teach the expression of two proteins, melamine deaminase which is 98% identical to atrazine chlorohydrolase but is functionally different (page 2405, Abstract). Furthermore, Seffernick et al. teach that though the structure of proteins with similar sequence identity may also be similar, the functions of the proteins are not predictable, as in the example of two proteins with 56% sequence identity, similar three dimensional structure but that do not catalyze the other's reaction (page 2409, col. 1, par 3).

(7) It is highly unpredictable if the combination of domains listed in the specification will successfully lead to an autoregulating protein where the input domains interact with each other and regulate the output domain. Though the idea of creating such a protein is expressed in the specification, there is insufficient evidence that the protein is enabled for all possible domains. Baker et al. teach that in order to determine protein structure, the sequence should have higher than 30% sequence identity to an already known structure (page 95, col. 2, par 1). Since, the instant application is directed to autoregulated fusion proteins that have not been taught in the prior art and are not taught as having being made (except for one example) by the specification, there is no sequence or known structure with which to make a comparison for structure prediction. Thus is not possible, based on an unavailable sequences and similar template sequences for comparison, to predict the actual structure and/or function of the resulting autoregulated fusion protein from the domains listed in the specification or any domain, for that matter, or whether the fusion the domains will result in a successfully functioning autoregulated protein.

Furthermore, re-iterating the teachings in the above cited prior art, fusion protein construction is highly unpredictable and functionality may be altered depending upon the construct development. This would lead to destroying the function of the protein in many instances. In the absence of factual evidence characterizing the structural and functional components of each and every fusion protein, as is instantly claimed, the effects of the changes to protein domains is largely unpredictable as to which ones of the claimed input and output will have a significant effect and which ones will not, thus requiring undue experimentation.

(8) The breath of the claims are broad.

The skilled practitioner would first turn to the instant description for guidance in making and using the claimed invention. However, the description lacks clear evidence that any combination of domains, other than the N-WASP, PDZ, and SH3, will successfully lead to an autoregulating protein where the input domains interact with each other and regulate the output domain. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss autoregulated fusion proteins comprising output domains and input domains where the input domains interact with each other to allostericaly and external ligand-dependently regulate the output domain. The prior art does teach, however, the unpredictability of altering protein domains. Finally, said practitioner would turn to trial and error experimentation to determine the proper relationships for input and output domains that will perform protein self-regulation as claimed. Such amounts to undue experimentation.

**(10) Response to Argument**

**A. Summary of Appellant's Position**

The test for enablement is whether the specification enables one skilled in the art to practice the invention as claimed without undue experimentation. Appellants have provided in their specification input and output domains that are not normally related but can be made into a fusion protein to provide protein signaling switching analogues to logic gates with diverse and novel input/output properties. The selection of input and output domains is discretionary, so long as the selected domains interact to provide the requisite ligand-dependent gating of the output domain (e.g. Specification, p. 6, lines 13-15 and p. 7, lines 18-19). In other words, making an autoregulating fusion protein is enabled because one of skill in the art would know which input and output domains to used in making the fusion protein and thus Appellants have satisfied the requirements for 35 U.S.C. 112, first paragraph (Brief page 3).

**B. Appellant's Arguments**

Appellant's argue that the test for enablement is whether the specification enables one of skill in the art to practice the invention as claimed without undue experimentation (Brief, p. 3, ¶ 1).

Appellants argue the potential of generating auto regulated fusion protein from input and interacting domains from data bases as well as mutating domains to provide binding partners (Brief, p. 4, ¶ 2).

Appellants argue that a wide variety of external ligands may be used to activate the switches by interacting with one or more of the input domains (Brief p. 5, ¶2).

Appellants argue that the specification "enables one skilled in the art to make and use without undue experimentation an autoregulated fusion protein comprising an output domain and a plurality of input domains (Brief, p. 6, ¶ 1).

Finally, Appellants argue that if one of skilled in the art engages in trail and error experimentation to practice a claimed invention does not necessarily amount to undue experimentation.

**Response to Arguments**

In response, the argument presented is not directed to the merits that form the basis of the instant scope of enablement rejection. While some embodiments of the claim are acknowledged as enabled, one of skill in the art must resort to undue experimentation in order to discern the enabled embodiments of the claim from the non-enabled embodiments, for example for various in put and output domains recited in the disclosure (specification, page 6, line 20 to page 7, line 14).

Though Appellants argue the potential exists to generate auto regulated fusion protein from various inputs and interacting domains from data bases, as well as mutating domains to provide binding partners, it is maintained that undue experimentation is required to determine whether the claim is enabled for the numerous possibility of domains.

In response to Appellant's argument that wide variety of external ligands may be used to activate the switches by interacting with one or more of the input domains, it is noted that applicants provide no evidence in the disclosure that the "wide variety" of autoregulating fusion proteins derived from the variety of domains and external ligand regulators are enabled.

Appellants argue that the specification enables one skilled in the art to make and use, without undue experimentation, an autoregulated fusion protein comprising an output domain and a plurality of input domains. However, Appellant only provides evidence of success with one combination of domains (i.e. N-WASP output domain, SH3 and PDZ input domains). The enablement of a general autoregulating fusion protein, however, is not enabled as evidenced by the teachings in the prior art, as stated above.

Finally, in response to Appellant's argument that if one of skilled in the art engages in trail and error experimentation to practice a claimed invention does not necessarily amount to undue experimentation, it is noted that Appellant's own work provides evidence that undue experimentation was required.

For example, see the post-filing art of Dueber et al., "Reprogramming Control of an Allosteric Signaling Switch Through Modular Recombination," (Science, 2003 vol. 301, pages 1904-1908), which teaches that the length of the linker between input and output domains affected switch behavior by making the switch more sensitive, indicative of reduced coupling of domains. However, within a certain library, increasing interdomain linker length did not uniformly reduce coupling and suggest that these

effects are **context-dependent** (page 1906, col. 1, ¶ 6 to col. 2, ¶ 1), which in turn suggest undue experimentation to determine the length of the linker needed for desired results. Dueber et al. further teach that the combinatorial switch library yielded switches with "**unexpected behavior'** of antagonistic or negative input control in which the PDZ ligand acted as an activator (page 1906, col. 3, ¶ 2).

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Anna Skibinsky, Ph.D.

Examiner

Art Unit 1631

LORI A. CLOW, PH.D.
PRIMARY EXAMINER
Lori A. Clow
11/13/2007

Conferees:

Marjorie Moran/Supervisory Patent Examiner

Gary Benzion, Ph.D./Supervisory Patent Examiner

Lori A. Clow, Ph.D./Primary Examiner

MARJORIE A. MORAN
SUPERVISORY PATENT EXAMINER
Marjorie A. Moran
11/13/2007

Gary Benzion
GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600